

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

THIS PAGE BLANK (USPTO)



PCT/GB 00 / 0 1 2 3 3



INVESTOR IN PEOPLE

GB 00 / 01933

The Patent Office
Concept House
Cardiff Road
Newport
South Wales

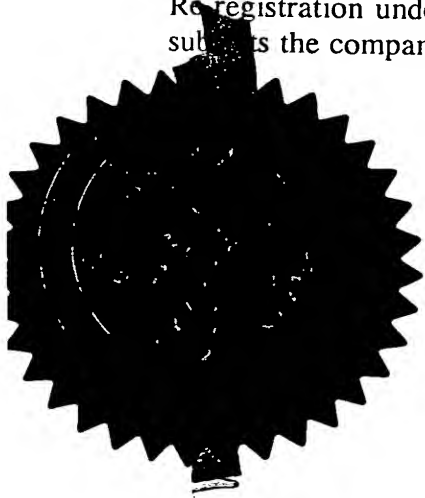
NP10 8QQ	
REC'D 03 JUL 2000	
WIPO	PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

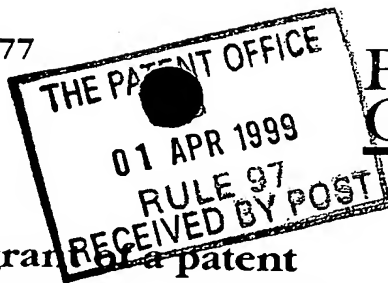
Dated

14 JUN 2000

**PRIORITY
DOCUMENT**

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

THIS PAGE BLANK (USPTO)



The Patent Office

1/77

06APR99 E437380-3 D02820
-----PD1/7700 0.00 - 9907596.2

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

Request for grant of a patent

(See instructions on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference

P02475GB

2. Patent application number

(The Patent Office will fill in this part)

9907596.2

3. Full name, address and postcode of the or of each applicant (underline all surnames)

HENDERSON MORLEY LIMITED
METROPOLITAN HOUSE
2 SALISBURY ROAD
BIRMINGHAM B13 8JS

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

GB

7635940001

4. Title of the invention

ANTIVIRAL COMPOSITION

5. Name of your agent (if you have one)

LAURENCE SHAW & ASSOCIATES

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

5TH FLOOR, METROPOLITAN HOUSE
1 HAGLEY ROAD
EDGBASTON
BIRMINGHAM B16 8TG

Patents ADP number (if you know it)

1362300

✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

YES
AT

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description	13
Claim(s)	1
Abstract	0
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature Laurence Shaw & Associates Date 31.3.99

LAURENCE SHAW & ASSOCIATES

12. Name and daytime telephone number of person to contact in the United Kingdom

LAURENCE SHAW : 0121.454.4962

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*
- Write your answers in capital letters using black ink or you may type them.*
- If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*
- If you have answered 'Yes' Patents Form 7/77 will need to be filed.*
- Once you have filled in the form you must remember to sign and date it.*
- For details of the fee and ways to pay please contact the Patent Office.*

DUPLICATE

Agent's Ref: PO2475GB

ANTIVIRAL COMPOSITION

The invention relates to an anti-viral composition useful in the therapeutic or prophylactic treatment of a range of viral conditions. More particularly the invention is applicable to the treatment of Herpes viral infections.

It has been suggested that certain marine algal species have anti-viral activity, for example, Ehresmann, 1977, J Phycol. 13:37-40. However, the species so far identified as having anti-viral action have been both rare in their occurrence and difficult to harvest as well as being impossible to grow in culture. This has limited their usefulness.

The invention is based on the realisation that extracts of *Palmaria palmatum* are useful for the purpose specified. *Palmaria palmata* is different in that it is abundant, may be artificially cultured and therefore, may be used more easily to mass produce an anti-viral material.

In one aspect the invention provides a water soluble extract of *Palmaria palmata* for use as a medicament.

In another aspect the invention provides a water soluble extract of *Palmaria palmata* as an antiviral agent.

In another aspect the invention provides a composition comprising the water soluble extract for use as a medicament.

The composition may be formulated for application in any suitable way, e.g. as a capsule, a tablet, suppository, injectable solution, topical cream; or the like.

In yet another aspect the invention provides a method of treating herpes virus infections in human or animal subjects, comprising applying to the subject a water soluble extract of *Palmaria palmata*. Preferably the application is ingestion.

The rate of application may be determined by routine experimentation.

The water soluble extracts of *Palmaria palmata* are extremely effective for the treatment of viruses of the herpes family including herpes simplex type 1, herpes simplex type 2, varicella zoster cytomegalovirus, human herpes type 6 and human herpes type 8. The anti-viral activity of these water soluble extracts may also be effective against other viruses.

Biochemical analyses of *Palmaria palmata* show that the major components are as follows:

Protein. The classical Kjeldahl method support a high protein content of *Palmaria palmata*.

Lipids. Lipids may be extracted using a solvent into which lipids dissolve, e.g. chloroform.

Minor components include vitamins and minerals including carotene, ascorbic acid, calcium, iron, and iodine.

Carbohydrates:

The carbohydrate fraction of *Palmaria palmata* contains easily soluble polysaccharides and more fibre like polymers which act similarly to cellulose. It is possible to fractionate the carbohydrates found in *Palmaria palmata* by extraction/precipitation.

While we do not wish the invention to be limited by the following theory our evaluations suggest that as the carbohydrate fraction is the only major water soluble component of the algae, the anti-viral action is from a complex carbohydrate and most probably polysaccharide in nature. The present knowledge of complex carbohydrates does not enable the large scale production or manufacture of these very complex molecules. For this reason it is believed that for a pharmaceutical compound to be successfully derived from *Palmaria palmata*, it will be extracted from cultured plants.

A sample of *Palmaria palmata* (Linnaeus Kuntze) belonging to the family Rhodophyta (Common name Dulse, Dillisk, Dilleasc, Creathnach) was harvested from the sea and identified as *Palmaria palmata* by the National University of Ireland in Galway, Department of Marine Biology, Ireland, using molecular biology techniques to specifically identify the genome of *Palmaria palmata*. This was confirmed by the physical appearance of the specimen conforming to that expected. This seaweed has a reddish brown colour with membranous or leathery flattened fronds 50 – 300 mm long arising from a discoid base usually with a small stipe expanding to form a simple or dichotomously and palmately divided fronds often with characteristic marginal leaflets. This seaweed may be found in many

oceans attached to rock, mussels in intertidal or shallow subtidal waters. it is widely distributed and abundant.

Palmaria palmata may be cultivated for harvesting in any suitable way. We envisage that portions of the plant will be attached to ropes or tubes in sites having strong tidal currents but which are sheltered from excessive wave action. An alternative way may be to cultivate the plants in tanks having controlled concentration of essential nutrients and possibly using heated waste water.

Once harvested, the sample of *Palmaria palmata* was subsequently dried at 3 temperatures, namely 4°C, 25°C and 65°C, to a water content of approximately 10%. Once dried the algae may then be comminuted by any suitable method (use of pestle and mortar or liquidiser) to a fine powder. This powder may then be stored at room temperature or indefinitely at - 20°C prior to use. The powder is mixed with sterile purified water and shaken periodically either manually or by a proprietary shaker and subsequently left overnight in a fridge. The resultant mixture is then centrifuged at 3000 rpm for 30 minutes and the supernatant is kept for further analysis and experimentation.

It is preferred that the dried algal powder be present in the proportions of the order of 50 g *Palmaria palmata* and 300 mls water. The aqueous extract is preferably sterilised by passage through a proprietary millipore or other bacterial filter.

The Herpes Simplex Virus

The herpes simplex virus (HSV) is a large (150 – 200nm) DNA virus which consists of approximately 152,000 base pairs of double stranded DNA encapsulated in a proteinaceous capsid. The capsid is surrounded by a less well defined structure known as the tegument. The virus is contained in a host cell derived lipid bilayer which is studded with virus specific glycoproteins and integral membrane proteins.

Genital Herpes

Recurrent herpes genitalis is estimated to affect over 45 million people in the USA alone. (Fleming et al NEJM Oct 97). The incidence is increasing, leading to a massive reservoir for transmission of infection to sexual partners and new-born infants. Once infected, over 95% of patients who have proven primary herpes genitalis have had at least one recurrence with an average of 5 – 6 recurrences per year. Approximately 25% of people will have recurrences at monthly intervals accompanied by extremely troublesome physical discomfort and (often) psychological upset. Current therapy for genital herpes revolves around psychological support, education, barrier methods of contraception and treatment on a regular basis with the expensive anti-viral drugs such as Aciclovir, Penciclovir and Famciclovir. These are not tolerated by all sufferers and in some cases are ineffective.

Genital Herpes in Pregnancy

Herpes simplex infection may be spread from mother to foetus. This usually occurs during parturition but can rarely occur in-utero. The rate of transmission depends on whether the mother is suffering primary herpes, where the transmission rate is 50% or recurrent herpes where the transmission rate is 8%.

If any lesions are visible during the onset of labour, this would be an indication for undertaking a caesarian section.

Neonatal Infection

50 – 60% of infants with neonatal Herpes simplex virus infection are born to mothers with no history of genital herpes infection. Neonatal herpes simplex virus infection is very serious. Over 70% of cases present infections localised to the eyes, skin or mouth within 3 – 30 days of birth. Unfortunately, over three quarters of those infected will progress to disseminated or CNS involvement which carries a very high morbidity and mortality.

Herpes Encephalitis

Acute encephalitis caused by herpes simplex virus is a common and often fatal infection. The herpes viruses have a role in other pathology.

(i). Neurological Diseases: Bells Palsy

There is now compelling evidence to suggest that Bells palsy is caused by an acute herpes simplex infection of the facial nerve. In a study by Murakami (Annals of Internal Medicine 124 pt 1 27 – 30, 1996 Jan) PCR of endoneural fluid revealed HSV genomes in 11/14 patients while in healthy controls and those with Ramsay Hunt syndrome the virus could not be detected. A recently published placebo controlled double blind trial treating those with Bells palsy with either prednisolone alone or prednisolone with acyclovir showed a very statistically superior outcome when using acyclovir leading the researchers to suggest that bells palsy is probably caused by herpes simplex. (Adour et al Annals of Otolaryngology and Rhinology 105 (5) 371 – 8 May 1996).

(i). Senile Dementia and Organic Brain Disease

As early as 1975 a link between herpes simplex and senile dementia was suggested. (Libikova Acta Virologica 19(6) : 493 - 5, 1975). In this study, 47% of patients suffering with senile dementia had neutralising antibodies to HSV 1 in their cerebrospinal fluid, compared to none of mentally retarded adolescents. Serum levels of antibodies were elevated in 61% of demented patients compared with 31% of normal controls. More recent work (Jamieson et al Journal of Pathology 167(4) : 365 - 8 Aug 1991) used PCR (polymerase chain reaction) to detect thymidine kinase from viral DNA. There was a significant anatomically specific presence of herpes simplex in the brains of those with senile dementia with virus being commonly detected in the hippocampus and the cortex but universally absent in the occipital cortex.

(iii). Inflammatory Bowel Disease

An interesting study by Wakefield (Journal of Medical Virology 1992 Vol. 38 3 : 183 - 190) demonstrated herpes virus DNA in the large intestine of biopsy specimens from patients with ulcerative colitis and Crohns disease. It appeared that the presence of at least two herpes viruses were needed to cause pathology.

(iv). Malignancy

A study by Ruther (Tumordiagnostik & Therapie 1994 Vol. 15 No 14, pp 121 - 127) examined biopsy specimens from patients with bronchial carcinoma, pleural mesothelioma, sarcoid and asthma. He found a significant proportion were infected with several herpes viruses (HSV 1 and 2, HHV 6 and EBV) compared to no detectable virus in healthy controls. He suggested that because viruses of the

herpes group can play a part in malignant transformation of cells, the role of these viruses as causative agents of malignant diseases in man should be investigated further.

(v). Lymphoproliferative Disorders

It has been known for many years that the herpes virus Epstein Barr is the causative agent in some forms of lymphoma. Further work examining a rapidly fatal lymphoproliferative disorder in bone marrow transplant recipient (Brion et al Nouvelle revue Francaise hematologie 1995 37 6 pp 289 – 296) showed that herpes virus genome was present in tumoral cells of all analysed specimens including herpes simplex type 1.

All of the above suggest that the role of Herpes simplex virus is not only extremely widespread within the general population but its pathological effects can be just as diverse highlighting the urgent need for effective treatments. It is considered that this invention will provide such effective treatments.

In order that the invention may be well understood it will now be described by way of illustration only with reference to the accompanying examples.

EXAMPLE 1

50 g of *Palmaria palmata* was dried at 65°C in air and the resultant dried plant material was comminuted in a domestic blender. The comminuted plant matter was then mixed with 300 ml of water at 19°C which had been purified by passage

through a Bobby Sterilising Double Distill water purifier. This was then stirred by manual agitation and left overnight at 4°C. The resultant mixture was centrifuged at 3000 rpm for 30 minutes in a proprietary centrifuge. The supernatant was then removed and passed through a millipore bacterial filter to remove any particulate or bacterial contamination. The resultant clear, pink/purple coloured liquid contains the active substance. The liquid was removed from the active compound by freeze drying using a proprietary freeze drier (e.g.) Edwards Modulyo EF4). The resultant powder has a pinkish colour. This was then encapsulated in a standard gelatin capsule at a concentration of 200 mg per capsule. This encapsulated *Palmaria palmata* extract was then administered to a patient as described below.

Human Subject

A male human diagnosed as having recurrent type 2 genital herpes by culture of virus from the penile lesion by polymerase chain reaction showing type 2 herpes simplex genome, and the presence of type 2 specific IgG against herpes simplex gG2 confirms that this was recurrent rather than primary genital herpes infection. The subject was prone to frequent (usually monthly) and severe recurrences of genital herpes. The subject has suffered from these for the previous 12 years and had tried several anti-viral drugs which had proven either unhelpful or unsuitable. The outbreaks would always cause a vesicular penile eruption with typically 12 blisters on the shaft of the penis. These so-called prodromal symptoms would inevitably yield a full attack. Within 48 hours of developing the lesions, glands would swell in the groin and systemic symptoms of viraemia would develop (e.g. raised body temperature, achy joints and tiredness). The lesions on the penis would heal without scarring after approximately 14 days.

On three separate outbreaks this subject was administered by ingestion the capsules containing the freeze dried extract of *Palmaria Palmata* at a dose of 200 mg capsule, three times daily for 5 days, taken as soon as symptoms of the prodrome developed. The subject described that on each occasion of the 3 outbreaks where he administered the extract during the prodromal phase, symptoms improved within 2 hours. On two occasions the outbreak was aborted i.e. the tingling of the penis did not produce the expected vesicular rash. There was no associated swelling of glands in the groin. On the occasion that the outbreak was not aborted, the attack was much less severe than normal. Only 6 lesions were evident, no swelling of groin glands was noted and no systemic symptoms were reported. Time to full healing was 6 days.

EXAMPLE II

Bioassays with herpes simplex virus in vitro were undertaken to follow the anti-viral activity of the water extract of *Palmaria palmata*. Culture and assay methods follow those described in Lennette and Schmidt (1979) for herpes simplex virus and Vero cells with minor modifications.

Herpes simplex strains used

Type 1 herpes simplex strain HFEM is a derivative of the Rockerfeller strain HF (Wildy 1955) and Type 2 herpes simplex strain 3345 a penile isolate (Skinner et al 1977) were used as prototype strains. These prototypes were stored at high multiplicities of infection at -80°C until needed.

Cell Cultures

African Green Monkey kidney cells (Vero) were obtained from the national Institute of Biological standards and Control UK and were used as the only cell line for all experiments in this Example.

Culture Media

Cells and viruses were maintained on Glasgows modified medium supplemented with 10% foetal bovine serum.

50g *Palmaria palmata* were dried at 65°C, comminuted in a domestic blender, mixed with 300 mls water and left overnight at 4°C and centrifuged at 3000 rpm for 30 minutes. The supernatant was removed and following sterilisation via a millipore filter subsequently diluted 1 in 5 with purified water (the stock solution).

The effects of this stock solution on Vero cells in culture was examined, as were the effects of Vero cells which had been infected with type 1 and type 2 virus at varying levels of infectivity. The effect of the stock solution on extracellular virus was also examined.

Results

The stock solution was found to show only minor inhibition of Vero attachment and growth and showed moderate cytopathogenesis as adjudged by the morphology of cell culture. This suggests that the water soluble extract of *Palmaria palmata* has only minimal cytotoxic effects.

The effects of the stock solution on different multiplicities of infection (i.e. concentration of virus) may be summarised as below:

Inhibition of hsv2 cytopathic effect.

Multiplicity of infection (Dose of virus)	Effect of Stock Solution
High	++++
Medium	++++
Low	++++

++++ signifies inhibition of virus cytopathic effect i.e. the action of the virus on destroying the vero cells was prevented.

This example demonstrates that virus activity was prevented by applying a small volume of stock solution to Vero cells infected with virus. Other examples have shown that at lower concentration of stock solution e.g. diluted 1 in 25, 1 in 50, 1 in 100, this anti-viral activity disappears in a concentration dependent manner. Other examples examined the effect on Herpes Simplex type 1 and other herpes viruses with almost identical results.

EXAMPLE III

Further experiments were conducted to examine effects on extracellular virus. There was no direct virucidal activity on extracellular virus. This result supports

the claim that a water soluble extract from *Palmaria palmata* contains anti-viral activity.

CLAIMS

1. A method of treating herpes virus infections in subjects (human and animal) comprising the ingestion of a water soluble extract of *Palmaria palmata*.
2. A composition useful for the treatment of herpes virus infections in subjects comprising an effective antiviral amount of the composition in Claim 1 and a suitable carrier.
3. A composition in accordance with Claim 2, adapted for topical application.
4. A composition in accordance with Claim 2, adapted for systemic application.